

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208254Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Office of Clinical Pharmacology Review

<b>NDA Number</b>	208-254
<b>Link to EDR</b>	<a href="#">EDR link</a>
<b>Submission Date</b>	02/28/2017
<b>Submission Type</b>	NME; Standard Review
<b>Brand Name (Proposed)</b>	Rhopressa™
<b>Generic Name</b>	Netarsudil (AR-13324)
<b>Dosage Form and Strength</b>	Ophthalmic solution 0.02%
<b>Route of Administration</b>	Topical ocular
<b>Proposed Indication</b>	For treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
<b>Applicant</b>	Aerie Pharmaceuticals Inc.
<b>Associated INDs</b>	IND 113,064
<b>OCP Review Team</b>	Yongheng Zhang, PhD/Reviewer; Philip Colangelo, PharmD, PhD/Team Leader
<b>OCP Final Signatory</b>	John Lazor, PharmD / Office of Clinical Pharmacology Division IV Director

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## **1 EXECUTIVE SUMMARY**

Netarsudil (AR-13324) is a new molecular entity (NME), a Rho-associated protein kinase (ROCK) inhibitor formulated as a topical ophthalmic solution 0.02% for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). ROCK inhibitors represent a new class of potential glaucoma medications that lower IOP by directly increasing trabecular outflow of aqueous humor.

In support of the NDA, the Applicant submitted seven clinical studies, including two Phase 1 studies (AR-13324-CS101, AR-13324-CS102), three Phase 2 studies (AR-13324-CS201, AR-13324-CS202 & AR-13324-CS204), and two Phase 3 studies (AR-13324-CS301 & AR-13324-CS302).

The Phase 1 study AR-13324-CS101 is a pharmacokinetic study conducted in healthy subjects to assess the tolerability and safety of netarsudil ophthalmic solution 0.02%, as well as the systemic exposure of netarsudil and the primary active metabolite AR-13503. The clinical PK study demonstrated that the systemic exposures of netarsudil and the active metabolite are negligible following repeat topical ocular application of netarsudil ophthalmic solution 0.02%.

### **1.1 Recommendations**

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable, and the Clinical Pharmacology review team recommends approval of Rhopressa (Netarsudil 0.02% ophthalmic solution).

The reviewer's proposed labeling changes in Appendix 4.3 will be forwarded to the sponsor.

### **1.2 Post-Marketing Requirements and Commitments**

None.

## **2 Summary of Clinical Pharmacology Assessment**

### **2.1 Pharmacology and Clinical Pharmacokinetics**

Netarsudil is a potent inhibitor of Rho kinase that also has inhibitory activity against norepinephrine transporter. It is an ester prodrug with the 4-hydroxymethyl phenyl moiety esterified to increase the permeability of the active drug into the eye. *In vitro* studies of netarsudil metabolism by human corneal tissues confirmed that netarsudil is metabolized by corneal esterases to produce AR-13503, which is the active drug in aqueous humor and increases trabecular outflow of aqueous humor in perfused human eyes and causes dilation of episcleral veins.

The clinical PK study demonstrated the lack of systemic exposures to netarsudil and the active metabolite following repeat topical ocular application of netarsudil ophthalmic solution 0.02%.

### **2.2 Dosing and Therapeutic Individualization**

#### **2.2.1 General Dosing**

The applicant's proposed dosing is one drop in the affected eye(s) once daily in the evening.

#### **2.2.2 Therapeutic Individualization**

None.

### **2.3 Outstanding Issues**

None.

### **2.4 Summary of Labeling Recommendations**

The Applicant's proposed labeling with respect to clinical pharmacology related contents is generally acceptable; however, the reviewer has some recommended edits. Refer to Appendix 4.3 for the reviewer proposed edits.

### 3 Comprehensive Clinical Pharmacology Review

#### 3.1 Overview of the Product and Regulatory Background

Netarsudil (AR-13324) is a Rho-associated protein kinase inhibitor that also has inhibitory activity against the norepinephrine transporter. Netarsudil is being developed for the indication of reducing elevated IOP in patients with OAG or OHT.

For clinical use, netarsudil is formulated as netarsudil ophthalmic solution 0.02%, a sterile, isotonic solution at approximately pH 5, preserved with benzalkonium chloride.

Multiple meetings have been held between the Division and the Applicant throughout development, including the End of Phase 2 meeting (May 6, 2014) and the Pre-NDA meeting (October 27, 2015).

#### 3.2 General Pharmacology and Pharmacokinetic Characteristics

**Table 1:** Summary of clinical pharmacology and pharmacokinetics

Pharmacology	
<b>Mechanism of Action</b>	Netarsudil, a Rho kinase and norepinephrine transporter inhibitor, has been shown in animal and human studies to reduce IOP by multiple mechanisms of action: increasing trabecular outflow facility, decreasing the production of aqueous humor and reducing episcleral venous pressure
<b>Active Moieties</b>	Netarsudil is an ester prodrug that is metabolized in human cornea into the active metabolite, AR-13503
<b>QT Prolongation</b>	The IC <sub>50</sub> for the inhibitory effect of netarsudil on hERG potassium current was 0.4 $\mu$ M (i.e., 181 ng/mL), which is well above the plasma concentrations detected in the clinical PK study (see summary below). Thus, there is little to no potential of QT prolongation with topical ocular administration of netarsudil
General Information	
<b>Bioanalysis</b>	Validated HPLC/MS/MS methods to determine netarsudil and its metabolite AR-13503 in the plasma
<b>Healthy vs. Patients</b>	Systemic exposure to netarsudil and its metabolite AR-13503 assessed in healthy subjects only
<b>Drug exposure at steady state following the therapeutic dosing regimen</b>	The systemic exposure of netarsudil and/or the metabolite AR-13503 is negligible (i.e., mostly below the LLOQ) following repeat topical ocular administration (QD for 8 days) of 0.02% netarsudil Ophthalmic Solution in healthy subjects
<b>Range of effective dose or exposure</b>	According to the mean IOP reduction from baseline, netarsudil 0.01% was less effective than the netarsudil 0.02% and 0.04%; netarsudil 0.02% had similar efficacy but better tolerability compared to netarsudil 0.04%
<b>Maximally tolerated dose or exposure</b>	Netarsudil 0.04% QD
<b>Dose Proportionality</b>	Not determined
<b>Accumulation</b>	No systemic accumulation detected

<b>Variability</b>	Not applicable; plasma exposure mostly below LLOQ
<b>Absorption</b>	
<b>Bioavailability</b>	Negligible following topical ocular administration
<b>T<sub>max</sub></b>	NA
<b>Distribution</b>	
<b>Volume of Distribution</b>	NA
<b>Plasma Protein Binding</b>	Netarsudil > 97% bound at 10 µM; AR-13503 61% bound at 10 µM
<b>Substrate transporter systems [in vitro]</b>	Not studied
<b>Elimination</b>	
<b>Terminal Elimination half-life</b>	NA
<b>Effective Elimination half-life</b>	NA
<b>Metabolism</b>	
<b>Fraction metabolized (% dose)</b>	NA
<b>Primary metabolic pathway(s) [in vitro]</b>	Netarsudil is metabolized to AR-13503 by esterases in corneal tissues; No evidence of metabolism of AR-13503 incubated with liver microsomes
<b>Excretion</b>	
<b>Primary excretion pathways (% dose) ±SD</b>	Not determined in humans
<b>In vitro interaction liability (Drug as perpetrator)</b>	
<b>Inhibition/Induction of metabolism</b>	Netarsudil inhibits CYP 1A2, 2C19, 2C9, 2D6 and 3A4 >80% at 10 µM; AR-13503 inhibits CYP 2C19 and 2D6 >65% at 10 µM. (Note: raw data not reviewed)  There is minimal to no potential of systemic DDIs because of the negligible plasma concentrations of parent netarsudil and metabolite (AR-13503) detected following topical ocular administration.
<b>Inhibition/Induction of transporter systems</b>	Not studied

### 3.3 Clinical Pharmacology Review Questions

#### 3.3.1 Does the available clinical pharmacology information provide supportive evidence of effectiveness?

Yes. Two Phase 1 studies in healthy volunteers (AR-13324-CS101 & AR-13324-CS102), two Phase 2 studies (AR-13324-CS201 & AR-13324-CS202) and two Phase 3 studies in patients with OAG or OHT (AR-13324-CS301 & AR-13324-CS302) have been completed with netarsudil ophthalmic solution 0.02% compared to Placebo (vehicle; AR-13324-CS102 and AR-13324-CS201), latanoprost 0.005% QD (AR-13324-CS202), or timolol maleate ophthalmic solution 0.5% BID (AR-13324-CS301 and AR-13324-CS302).

The clinical pharmacokinetics study AR-13324-CS101 was an open-label, non-comparative, single-arm, single-center study with 18 healthy adult male or female subjects. Subjects received netarsudil ophthalmic solution 0.02% once daily for 8 days. There were no detectable plasma netarsudil concentrations above the lower limit of quantitation (LLOQ of 0.100 ng/mL) at any time point in any subject. Only 1 plasma concentration for the metabolite AR-13503 was detectable (at 0.11 ng/mL) for 1 subject on Day 8 at 8 hours post dose. Therefore, it is concluded that systemic exposure to netarsudil and the active metabolite is negligible following repeat topical ocular application of netarsudil ophthalmic solution 0.02%.

The optimal dose concentration of netarsudil for Phase 3 studies was established from the two dose-response Phase 2 studies. In the first study (AR-13324-CS201), 3 doses of AR-13324 (0.01%, 0.02% and 0.04%) and vehicle were dosed QD AM for 7 days. Based upon mean reduction in IOP from baseline, netarsudil 0.01% was less effective than the netarsudil 0.02% and 0.04% concentrations ; netarsudil 0.02% had similar efficacy but superior tolerability compared to netarsudil 0.04%.

In the second dose-response study (AR-13324-CS202), 2 doses of netarsudil (0.01% and 0.02%) were dosed QD PM and compared to latanoprost ophthalmic solution 0.005% after dosing for 28 days. Netarsudil 0.01% and 0.02% produced clinically relevant and statistically significant changes from baseline in IOP. The 0.02% concentration was numerically more effective than the 0.01% concentration at 8 of the 9 post-treatment time points. Therefore, netarsudil 0.02% was chosen for Phase 3.

QD and BID dosing of netarsudil 0.02% were evaluated in two Phase 3 studies, AR-13324-CS301 (QD only) and AR-13324-CS302 (QD and BID) for non-inferiority to BID dosing of timolol maleate ophthalmic solution 0.5%. The BID treatment arm was included following FDA's recommendation to demonstrate the relative effectiveness and safety of QD vs BID dosing with netarsudil. Based on the benefit-to-risk profiles, netarsudil 0.02% QD (PM) was proposed as the final dosing regimen.

**3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

Yes. Refer to 3.3.1.

**3.3.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?**

No. Given the negligible systemic exposure following topical administration, dose adjustment is not warranted in patients based on the commonly known intrinsic factors.

**3.3.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

No. Given the negligible systemic exposure to netarsudil and AR-13503 following repeat ocular dosing with netarsudil ophthalmic solution 0.02%, no clinically relevant drug-drug interactions are expected in the intended patient population.

## 4. Appendices

### 4.1 Clinical PK Assessment

#### 1. Title

An Open-Label Study Assessing the Ocular and Systemic Safety and Systemic Absorption of AR-13324 Ophthalmic Solution, 0.02% in Healthy Volunteers (Study # AR13324-CS101)

#### 2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by Aerie Pharmaceuticals, Inc from November 6, 2013 to November 14, 2013 with the final report date – March 7, 2014.

#### 3. Objectives

- To evaluate the ocular and systemic safety of AR-13324 Ophthalmic Solution, 0.02%.
- To evaluate the systemic exposure of AR-13324 Ophthalmic Solution, 0.02%.

#### 4. Trial Design

This was an open-label, non-comparative, single-arm, single-center study with 18 healthy adult male or female subjects. After a screening visit and confirmation of qualifications, subjects received AR-13324 Ophthalmic Solution 0.02% for 8 days. Treatment was administered in each eye (OU) one drop once a day (QD) in the morning (AM).

#### 5. Excluded Medications, Restrictions or Exceptions

NA.

#### 6. Rationale for Doses Used in the Trial

The dose used for this study was selected based upon preclinical safety studies and the results of two previous clinical studies, AR-13324-CS201 and AR-13324-CS202. The dose is also the same as that proposed in the label.

#### 7. Drugs Used in the Trial

AR-13324 Ophthalmic Solution, 0.02%, manufactured by Aerie Pharmaceuticals, Inc., Lot No.: 1590642.

#### 8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Blood samples were obtained for bioanalytical assessment of AR-13324 and its metabolite AR-13503 at the following times post dose on Day 1: 15 min, 30 min, 1, 2, 4, and 8 hours, and at the following times on Day 8: predoes (-30 min), 15 min, 30 min, 1, 2, 4, 8, and 23.5 hours post dose. The following PK parameters were presented for AR-13324 and its metabolite AR-13503 on Days 1 and 8, where applicable: AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, AUC%extrap, C<sub>max</sub>, t<sub>max</sub>, and t<sub>1/2</sub>.

##### *Bioanalytical method*

- Plasma concentration

Analyte	Matrix	Validation Report	Bioanalytical Report
AR-13324	Plasma	# TRTPR13-073	# TRTPR13-085
AR-13503	Plasma	# TRTPR13-073	# TRTPR13-085

Bioanalytical Method:

Method Type	LC-MS/MS	Matrix	K <sub>2</sub> EDTA Plasma
Analytes	AR-13324, AR-13503		
Range	0.1-100 ng/mL		

Validation	▪ Method validated prior to use	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA
	▪ Method validation acceptable	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
	▪ Quality control sample range acceptable	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
	▪ Chromatograms provided	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
	▪ Accuracy and precision of the calibration curve acceptable	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
	▪ Accuracy and precision of the quality control samples acceptable	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
	▪ Incurred samples analysis is acceptable	<input type="checkbox"/> Yes <input type="checkbox"/> No Note: Not conducted
	▪ Overall performance acceptable	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Inspection	▪ Will the bioanalytical site be inspected	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## 9. Results

A total of 18 subjects were enrolled in the study, and all completed the study. There were 18 subjects included in safety and PK analyses.

Summary of Demographics and Baseline Characteristics

Trait		Overall N=18 (100%)
Gender, n (%)	Female	14 ( 78%)
	Male	4 ( 22%)
Race, n (%)	White	18 (100%)
Ethnicity, n (%)	Hispanic or Latino	11 ( 61%)
	Not Hispanic or Latino	7 ( 39%)
Age (yrs)	N	18
	Mean	47.6
	SD	16.48
	Median	46.5
	Minimum	24
	Maximum	74

Note: All percentages are based on the number of subjects listed in the column header, Treatment = AR-13324 Ophthalmic Solution 0.02% instilled once daily in the morning into both eyes for 8 days

There were no observed plasma AR-13324 concentrations above the lower limit of quantitation (LLOQ, 0.100 ng/mL) at any time point in any subject. Only 1 plasma concentration above the LLOQ for AR-13503 was observed for 1 subject on Day 8 at 8 hours post dose (0.11 ng/mL, LLOQ of 0.100 ng/mL).

There were no deaths or serious adverse events (SAEs) in this study and no subject was discontinued due to an AE. Sixteen (16, 89%) subjects in this study reported AEs. The most frequently reported AEs were conjunctival hyperemia (89% subjects), vital dye corneal staining (39% subjects), and headache (17% subjects). Ocular-related AEs considered related or possibly related to AR-13324 included conjunctival hyperemia, eye pruritus, visual impairment, and vital dye corneal staining. No clinically significant trends were observed regarding clinical laboratory results or vital sign assessments with respect to subject safety.

## **10. Sponsor's Conclusions**

There were no systemic safety issues of note in the present study. Cardiovascular parameters did not reveal any safety issues of concern. There were no issues of note in the ocular safety of AR-13324 as evidenced by biomicroscopy, ophthalmoscopy, or visual acuity measurement. Clinically and statistically significant reductions in IOP were observed in these normotensive subjects. Transient mild conjunctival hyperemia was observed in most subjects and mild corneal staining was noted less frequently. Only one plasma concentration very close to the LLOQ for its metabolite AR-13503 was observed for one subject on Day 8 at 8 hours post dose.

In conclusion, 0.02% AR-13324 Ophthalmic Solution dosed QD AM for 8 days produced little or no quantifiable systemic exposure to the parent compound or the known metabolite AR-13503.

## **11. Reviewer's Assessment**

The Applicant's conclusions are valid. The systemic exposure to AR-13324 (netarsudil) and/or the metabolite AR-13503 is negligible following topical ocular QD administration of 0.02% AR-13324 Ophthalmic Solution in healthy subjects.

## 4.2 In Vitro Metabolism

### 1. Title

In vitro metabolism of AR-13324 (Study # AR13324-IRK03; Report date Jan 10, 2012)

### 2. Objectives

To characterize the metabolism of AR-13324 in liver microsomes of several commonly studied species, in liver S9 fractions from human and Aroclor-1254 induced Sprague-Dawley rat, as well as in cornea and plasma from several species.

### 3. Study Design

#### *Metabolism of AR-13324 by liver microsomes/S9 fraction*

AR-13324 metabolism was tested in the following liver microsomes/S9 fraction preparations: male and female beagle, male and female Cynomolgus monkey, male and female CD-1® mouse, male and female Sprague-Dawley rat, male New Zealand White rabbit, and pooled male and female human liver microsomes (b) (4)

#### *Metabolism of AR-13324 by isolated corneal tissues*

Enucleated pig eyes were harvested at a local abattoir (b) (4) within one hour of slaughter. Intact globes were stored on ice and used within 4 hours of slaughter. Measures were taken to prevent dehydration and abrasion of the corneal epithelial layers when dissecting the cornea from the globe. Intact globes were similarly harvested from dog (Beagles, (b) (4); study report AR-12286-AS02, Eye Tissue Collection, p.23), rabbit (Dutch Belted, (b) (4)), and monkey (Cynomolgus monkeys, (b) (4) study report AR-12286-AS13) . The intact globes were stored in K-Sol corneal preservation buffer under cold conditions and used within 24 hours of sacrifice. Human corneas were acquired from (b) (4) Human corneas were harvested and preserved according to current tissue banking procedures. Human corneal tissues acquired were viable, but rejected for transplant due only to serological incompatibility. Dog, rabbit, monkey and human corneal tissues were all handled identically to pig corneal tissue during the preparation and metabolism studies.

#### *Metabolism of AR-13324 by plasma of various species*

Pooled, mixed gender plasma from Cynomolgus monkey (Lot# BC041611PM1), human (Lot# BC041611PM2), rat (Lot# S-106903), rabbit (Lot# S-106902) and dog (Lot# 106901) were obtained from (b) (4)

### 4. Results

When incubated with liver microsomes from several species, AR-13324 underwent ester cleavage to form the metabolite, AR-13503.

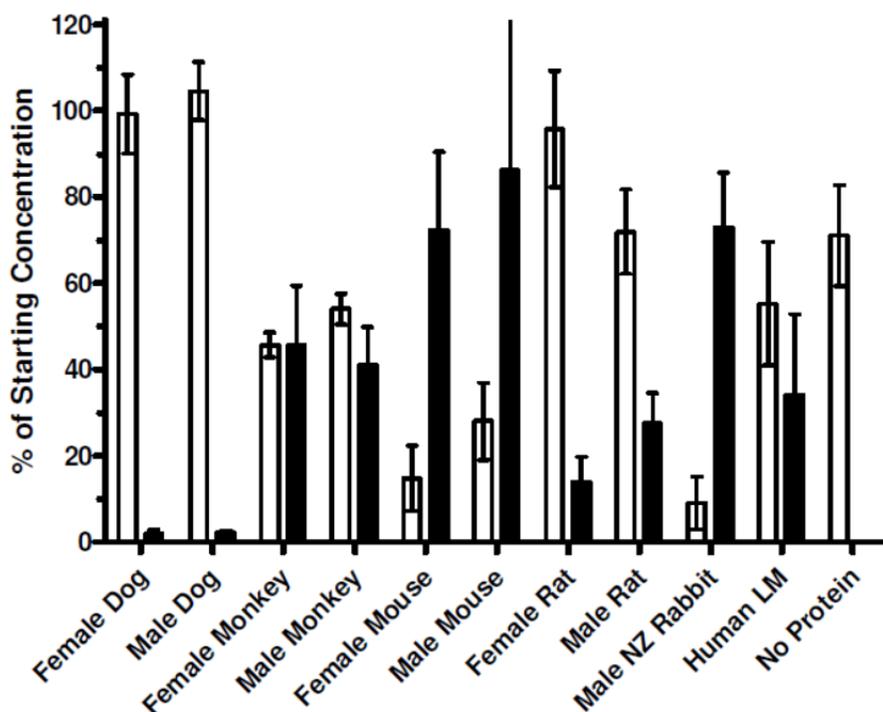


Figure 1: Metabolism of AR-13324 by liver microsomes of several species. Open columns represent AR-13324, and solid columns represent the esterase cleavage product AR-13503. The incubation time was one hour at 37 C.

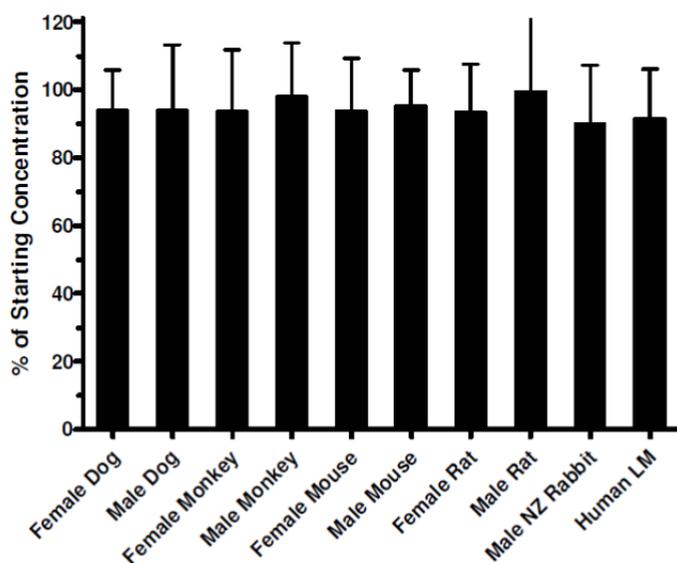


Figure 2: Metabolism of AR-13503 by liver microsomes of several species. The incubation time was one hour at 37 C.

To identify metabolites that may be produced in the eye upon topical ocular administration, AR-13324 was incubated with corneal tissue from various species for 4 hours at 37°C. Active metabolism of AR-13324 was observed in all species during the 4-hour exposure to corneal tissues. Since the size of corneal tissues varied between species, the rate at which AR-13324 was metabolized by esterases to produce AR-13503 was normalized to a 7-mm circular section of cornea (surface area of 39 mm<sup>2</sup>).

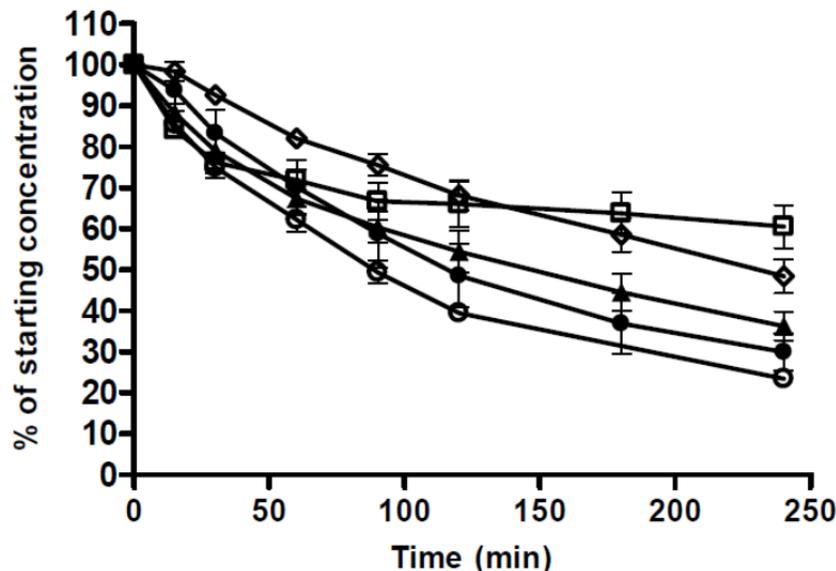


Figure 3: Metabolism of AR-13324 by corneas of various species at 37°C  
 -●-: DB Rabbit (n=3); -□-: Pig (n=3); -□-: Beagle (n=3); -□-: Human (n=3); -□-: Cyno (n=4)

AR-13324 metabolism was also studied in plasmas of 5 species during a 3-hour exposure. No obvious metabolism of AR-13324 was observed during the 3 hour exposure to Cynomolgus monkey, human, rat or dog plasma. In contrast, AR-13324 was rapidly metabolized when incubated with rabbit plasma.

### 5. Sponsor's Conclusions

During the course of one-hour incubation with liver microsomes, AR-13324 underwent ester cleavage to form the metabolite, AR-13503. This hydrolysis proceeded most rapidly with male New Zealand Rabbit microsomes (91% metabolized) and slowest with beagle microsomes (-4.6% and 9.2% metabolized for male and female beagle microsomes, respectively). When AR-13503 was incubated directly with liver microsomes, no evidence of metabolism was obtained for all species tested.

AR-13324 was rapidly metabolized by human liver S9 extract to produce AR-13503. AR-13503 did not undergo further metabolism in human S9 extract. Arochlor-Induced Rat liver S9 extract hydrolyzed AR-13324 at a much slower rate compared to human S9 extract and was also unable to directly metabolize AR-13503.

Active corneal metabolism of AR-13324 was observed in all species during the 4-hour exposure to corneal tissues. The results showed that the metabolism was most rapid in dog corneas ( $t_{1/2} = 98$  min), followed by monkey corneas ( $t_{1/2} = 109$  min), rabbit corneas ( $t_{1/2} = 140$  min), pig corneas ( $t_{1/2} = 156$  min), and human corneas ( $t_{1/2} = 175$  min).

While rapid metabolism was observed for AR-13324 in rabbit plasma, no metabolism was observed in plasma from human, dog, monkey and rat during the course of two-hour incubation.

### 6. Reviewer's Assessment

The sponsor's conclusions appear valid. AR-13324 can be metabolized via ester cleavage to the active metabolite AR-13503 by human liver microsomes, S9 extract, and corneas, but not in human plasma under the specified experimental conditions.

### 4.3 Proposed Package Insert (Original and Annotated) with Clinical Pharmacology Edits

Note: addition as underline; deletion as ~~strike through~~

#### 12.3 Pharmacokinetics

##### Absorption

(b) (4)

The systemic exposures of netarsudil and its active metabolite (AR-13503) were evaluated in 18 healthy subjects after topical ocular administration of RHOPRESSA 0.02% once daily (one drop bilaterally in the morning) for 8 days. There were no quantifiable plasma concentrations of netarsudil (lower limit of quantitation, LLOQ, of 0.100 ng/mL) post dose on Day 1 and Day 8. Only 1 plasma concentration at 0.11 ng/mL (LLOQ of 0.100 ng/mL) for the active metabolite was observed for 1 subject on Day 8 at 8 hours post dose.

##### Metabolism

(b) (4)

After topical ocular dosing, netarsudil is metabolized by esterases in the eye to the active metabolite (AR-13503).

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/s/  
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ABHAY JOSHI  
08/28/2017  
on behalf of Yongheng Zhang

PHILIP M COLANGELO  
08/28/2017

JOHN A LAZOR  
08/30/2017

# CLINICAL PHARMACOLOGY FILING FORM

## Application Information

<b>NDA/BLA Number</b>	208254	<b>SDN</b>	001
<b>Applicant</b>	Aerie Pharm Inc	<b>Submission Date</b>	08/30/2016
<b>Generic Name</b>	Netarsudil	<b>Brand Name</b>	Rhopressa (proposed)
<b>Drug Class</b>	A Rho kinase and norepinephrine transporter inhibitor		
<b>Indication</b>	For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension		
<b>Dosage Regimen</b>	One drop in the affected eye(s) once daily in the evening.		
<b>Dosage Form</b>	Ophthalmic eye drop solution; 0.02% netarsudil	<b>Route of Administration</b>	Topical ocular
<b>OCP Division</b>	IV	<b>OND Division</b>	DTOP
<b>OCP Review Team</b>	<b>Primary Reviewer(s)</b>	<b>Secondary Reviewer/ Team Leader</b>	
<b>Division</b>	Yongheng Zhang, Ph.D.	Philip Colangelo, Pharm. D., Ph.D.	
<b>Pharmacometrics</b>	-		
<b>Genomics</b>	-		
<b>Review Classification</b>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
<b>Filing Date</b>	10/29/2016	<b>74-Day Letter Date</b>	11/12/2016
<b>Review Due Date</b>	5/1/2017	<b>PDUFA Goal Date</b>	8/30/2017

## Application Fileability

**Is the Clinical Pharmacology section of the application fileable?**

- Yes  
 No

If no list reason(s)

**Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?**

- Yes  
 No

If yes list comment(s)

**Is there a need for clinical trial(s) inspection?**

- Yes  
 No

If yes explain

## Clinical Pharmacology Package

Tabular Listing of All Human Studies  Yes  No      Clinical Pharmacology Summary  Yes  No  
 Bioanalytical and Analytical Methods  Yes  No      Labeling  Yes  No

### Clinical Pharmacology Studies

Study Type	Count	Comment(s)
<b>In Vitro Studies</b>		
<input checked="" type="checkbox"/> Metabolism Characterization	1	Study AR-13324-IRK03 (human cornea and liver microsomes)
<input type="checkbox"/> Transporter Characterization		
<input type="checkbox"/> Distribution		

<input type="checkbox"/> Drug-Drug Interaction			
<b>In Vivo Studies</b>			
<b>Biopharmaceutics</b>			
<input type="checkbox"/> Absolute Bioavailability			
<input type="checkbox"/> Relative Bioavailability			
<input type="checkbox"/> Bioequivalence			
<input type="checkbox"/> Food Effect			
<input type="checkbox"/> Other			
<b>Human Pharmacokinetics</b>			
Healthy Subjects	<input type="checkbox"/> Single Dose		
	<input checked="" type="checkbox"/> Multiple Dose	1	Study# AR-13324-CS101 (qd; 0.02% for 8 days)
Patients	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
<input type="checkbox"/> Mass Balance Study			
<input type="checkbox"/> Other (e.g. dose proportionality)			
<b>Intrinsic Factors</b>			
<input type="checkbox"/> Race			
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input type="checkbox"/> Hepatic Impairment			
<input type="checkbox"/> Renal Impairment			
<input type="checkbox"/> Genetics			
<b>Extrinsic Factors</b>			
<input type="checkbox"/> Effects on Primary Drug			
<input type="checkbox"/> Effects of Primary Drug			
<b>Pharmacodynamics</b>			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<b>Pharmacokinetics/Pharmacodynamics</b>			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<input type="checkbox"/> QT			
<b>Pharmacometrics</b>			
<input type="checkbox"/> Population Pharmacokinetics			
<input type="checkbox"/> Exposure-Efficacy			
<input type="checkbox"/> Exposure-Safety			
<b>Total Number of Studies</b>		<b>In Vitro</b>	<b>In Vivo</b>
		1	1
<b>Total Number of Studies to be Reviewed</b>		1	1

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Study AR-13324-IRK03 (human cornea and liver microsomes)
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Study# AR-13324-CS101 (qd; 0.02% for 8 days); PK in healthy subjects
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Report # TRTPR13-073
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Dose-ranging evaluation in Study #AR-13324-CS201 (Phase 2: 0.01% and 0.02%), #AR-13324-CS202 (Phase 2: 0.01% and 0.02%), and AR-13324-CS302 (Phase 3: 0.02% qd and 0.02% bid)
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
<b>Complete Application</b> 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

previously agreed to before the NDA submission?		
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist</b>		
<b>Data</b>		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
<b>Studies and Analysis</b>		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Full waiver of pediatric studies requested (0 to 17 years of age)
<b>General</b>		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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YONGHENG ZHANG  
10/05/2016

PHILIP M COLANGELO  
10/07/2016